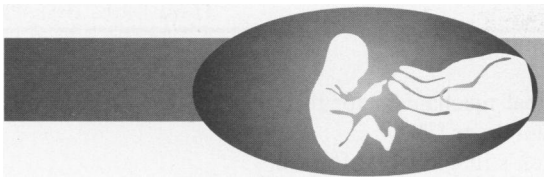

Fetal Drug Therapy

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Fetal drug therapy encompasses several areas, including the prevention of external genital masculinization in 21-hydroxylase deficiency syndrome (congenital adrenal hyperplasia), biochemical amelioration of methylmalonic acidemia, and biotin-responsive multiple carboxylase deficiency. The correction of cardiac arrhythmias has become relatively commonplace, and a reduction in the risks of neural tube defects is now possible with the use of preconceptual and early conceptual folic acid. Similarly, fetal function can be altered by the induction of fetal lung maturity using a number of agents; corticosteroids are the most common fetal pharmaceutic agent, and a number of other agents have also been tried. The most common route of administering pharmaceutic agents is through the mother and the placenta, although the direct administration of certain agents is becoming more common.

(Evans MI, Pryde PG, Reichler A, Bardicef M, Johnson MP: Fetal drug therapy, *In* Fetal Medicine [Special Issue]. West J Med 1993; 159:325-332)

Fetal surgical therapy has received international attention. The first successful repair of a diaphragmatic hernia in utero was the culmination of more than a decade of hard, tedious, and meticulous work.[1,2] There is still much work to be done developing surgical techniques, but the principles have been established.[3]

Despite the recent fanfare, fetal therapy is not new. Attempts to treat and reverse the abnormalities of fetal hemolytic disease came in the 1960s.[4] Intraperitoneal transfusions were used initially and by the 1970s had become a common form of intervention. In the late 1970s and throughout the 1980s, attempts at other surgical interventions of fetal disease, such as shunting obstructed bladders and hydrocephalus, and the first forays into open fetal surgery had been made.[2]

Although such dramatic fetal operations have received the most attention in the lay press, it should be recognized that some of the most important advances in fetal therapy have been pharmaceutic and that the future of fetal therapy will include the correction of genetic defects as well.[5(p236),6(p421)] We will review the spectrum of pharmaceutic interventions that reverse fetal structural abnormalities. We also will discuss the reduction of the incidence of neural tube defects with folic acid supplementation and strategies for preventing certain other structural anomalies. Finally, we will review the enhancement of fetal lung maturation with the use of corticosteroids and some proposed therapies for specific fetal biochemical alterations.

With the more advanced fetal diagnostic and interventional techniques, there is increased confidence about the ability to introduce agents into a fetus. The debate now moves to when and what to treat and, when treating with drugs, the best approach to administering them.

Transplacental Passage of Agents

Until recently the only approach to the pharmaceutic treatment of a fetus was transplacentally through the mother. With the introduction of high-resolution ultrasonography, the possibility of bypassing the placenta through direct invasive intra-amniotic, fetal intramuscular, or fetal intravenous administration has been realized and is being increasingly investigated.[7] The principal advantages of direct treatment are the avoidance of maternal toxicity and the metabolic effects of administered agents and the obviation of concern about the lack of placental permeability and transfer. It has been shown, for example, that the passage of cardiac agents across the placenta is less efficient in hydropic failure, thus rendering the sickest fetuses least likely to benefit (Table 1).[8]

When transfer characteristics of the intended therapeutic agents are favorable and possible maternal side effects are acceptable, the maternally administered transplacental route will probably continue to be the principal approach to fetal drug therapy. The efficiency with which a fetus can be so medicated will depend both on the rate of transfer of the drug from the mother to the fetus and the amount transferred after equilibrium across the placenta is reached. The placental transfer of pharmaceuticals and other chemicals is complex and remains an area of active investigation. The topic has been reviewed extensively by others[9,10] and will be only summarily discussed here.

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TABLE 1.—*Relative Advantages and Disadvantages of Transplacental and Direct Fetal Drug Therapy*

	Drug Route	
	Transplacental	*Direct*
Advantages		
Easy to give multiple doses		Bypasses "sick" placenta
Requires no procedural technical skill		Faster fetal uptake Can measure fetal levels
Disadvantages		
Dependent on placental function		Multiple invasive procedures
Maternal toxicity		Requires technical skill

Several experimental models, each having its own caveats, have been used in efforts to characterize the placental transfer of specific substances. The ideal model would be continuous concurrent in vivo pharmacokinetic evaluation of pregnant women and their fetuses after drug administration. Obviously such studies cannot be designed safely or ethically. Instead, for continuous and concurrent maternal-fetal drug evaluations, animal models have been substituted. The interpretation of data acquired from these studies, however, is limited by important differences in placental anatomy and maternal-fetal function between humans and available animals.[11] In vivo human studies have been restricted to efforts to measure maternal versus fetal blood concentrations of specific drugs either at the time of birth or during taking fetal blood specimens for other indications.[12] An alternative approach to evaluating human placental drug transfer is with in vitro preparations of dually perfused fresh human placenta.[13] This technique is hampered by the certainty of physiologic differences between a living intact placenta and an in vitro preparation regardless of how fresh.

The rate and extent of placental drug transfer varies considerably according to physiochemical properties of the substance and the complicated physiologic interaction of the fetal-maternal unit with the placenta at its interface (Table 2).[9] It is increasingly clear that essentially all exogenous substances including drugs, toxins, and nutrients are transferred to the developing embryo and fetus.[14] The common misconception of a "placental barrier" is outdated and misleading. Various specific transport systems operate across the placental exchange surface—active transport, facilitated transport, and pinocytosis—but simple diffusion is always involved and appears to be the principal mechanism for the transfer of most clinically relevant drugs.[9,10]

Fick's first law of diffusion,

$$\text{Rate of diffusion} = [K \times (C_m - C_f) \times SA]/d,$$

where K is the diffusion constant of the drug, $C_m - C_f$ represents the maternal-to-fetal concentration, SA is the exchange surface area, and d is the exchange membrane thickness, describes the relationships of the variables that govern the phenomenon of mass transfer by simple diffusion. From this equation it is apparent that placental drug transfer is driven by the principal force of a drug concentration gradient ($C_m - C_f$) across the exchange membrane. The rate of transfer is modified by placental characteristics (exchange surface area and thickness of the exchange surface membranes) and the physiochemical characteristics of the drug in question, which are represented by the diffusion constant K. Thus, a healthy placenta with a maximally intact exchange surface available and minimum diffusional distance will transfer a specific drug down a maternal-to-fetal concentration gradient much more efficiently than will a diseased placenta having either decreased exchange surface (perhaps due to multiple placental infarctions or the physiologic hypoperfusion that occurs in some hypertensive pregnant women) or increased diffusional distance (as may occur with placental edema in hydropic diseases). Similarly, a highly membrane-diffusible drug will be transported down a concentration gradient more effectively than will a less diffusible one.

The placental exchange surface can be thought of as a "lipoid barrier." Substances that are highly lipid-soluble tend to diffuse easily in a transcellular manner across the exchange membrane. In contrast, hydrophilic (water-soluble) substances are transferred poorly. The transfer of these drugs is negotiated through water-filled pores within the lipid membranes, a process that proves to be far less efficient. Other physiochemical characteristics of drugs that can profoundly influence placental transfer include molecular weight, ionization at maternal or fetal physiologic pH, and protein-binding characteristics.

Figure 1 shows four generalized models of maternal-to-fetal transplacental pharmacokinetics. Drugs having the properties of high lipid solubility, low ionization under physiologic conditions, and relatively low molecular mass (<1,000 daltons) will demonstrate rapid and exten-

TABLE 2.—*Principal Factors Influencing Transfer of Drugs From a Woman to Her Fetus*

Transfer	*Drug Factors*	*Placental Factors*	*Maternal Versus Fetal Factors*
Rate of transfer	Lipid solubility	Exchange surface area	Maternal-to-fetal concentration gradient
	Molecular weight	Exchange membrane thickness	Maternal and fetal placental perfusion
	Protein binding	Blood flow characteristics	
		Type of transfer*	
Extent of transfer	Degree of ionization	Type of transfer*	Maternal-to-fetal pH gradient
	Protein binding		Maternal versus fetal binding protein availability

*Passive diffusion is the principal mechanism of transfer, but facilitated and active transport mechanisms and pinocytosis may be involved in some cases.

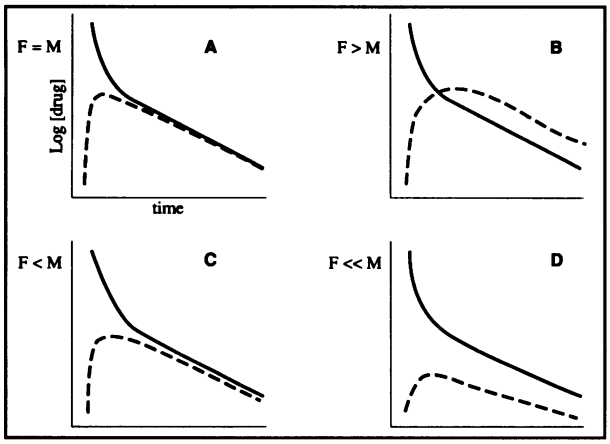

Figure 1.—The graphs represent 4 generalized models for fetal transplacental pharmacokinetics following a single maternal dose of prototype drugs: **A,** drugs in which fetal and maternal blood levels equilibrate; **B,** drugs in which fetal levels ultimately exceed maternal levels; **C,** drugs in which fetal levels are moderately or slightly less than maternal levels; and **D,** drugs in which fetal levels are nil or much less than maternal levels. See text for specific examples. Maternal blood levels are indicated by solid lines and fetal blood levels by broken lines.

sive transfer as shown in curve A. Examples of such drugs include most barbiturates, digoxin, phenytoins, ritodrine, and magnesium sulfate. Compounds that are hydrophilic, highly ionized, or of more substantial molecular weight (>1,000) will have much more limited rate and extent of placental transfer, as shown in curve B. Examples of such drugs are heparin (essentially "excluded" from exchange by its high molecular weight of approximately 1,200), quaternary ammonium compounds such as tubocurare, and succinylcholine (whose exchanges are profoundly limited by their high levels of ionization and water solubility), and erythromycin (exchange limited by high molecular weight and water solubility).

Other phenomena that can influence the ultimate transfer of certain drugs deserve mention. Placental metabolism could limit the transfer of an otherwise highly transferable compound. Cyclosporine, for example, is lipophilic but undergoes considerable metabolism during placental transfer, resulting in fetal concentrations about 50% of those of the mother. This drug would have a pharmacokinetic pattern as shown in curve C (Figure 1), despite its high membrane solubility. On the other hand, differential degrees of protein binding, or levels of drug ionization, in maternal versus fetal blood, as well as fetal urinary excretion with enteric recycling, can for some drugs result in fetal sequestration with levels actually exceeding those of the mother (as depicted in curve B). Examples of drugs sequestered by or of these mechanisms include penicillin, ampicillin, valproate, and many of the benzodiazepines.

Drug Treatment of Metabolic Defects

The potential for exogenous substances (drugs or ingested chemicals) to be transferred from a woman to her fetus is well known. In many cases, as with known teratogens such as thalidomide, phenytoin (Dilantin), and isotretinoin, the fetal effects can be adverse.[15] How the fetus responds to such exposures may be in part genetically determined.[16] Endogenous substances in the mother are likewise transferred to the fetus and in some cases may have similarly profound adverse fetal effects. Examples of fetal disorders caused by such "exposures" include diabetic embryopathy[17] and the extensive fetal damage seen due to untreated maternal phenylketonuria with resultant fetal hyperphenylalaninemia.[18]

For decades drugs and other products have been administered to pregnant women or directly to their fetuses in efforts to treat nonmetabolic fetal disorders or, in some cases, with the hope of improving the capacity for postnatal adaptation. Well-known examples include exchange transfusions for alloimmune hemolytic disease,* cardiac glycosides for fetal supraventricular tachycardia, and the administration of corticosteroids for the prevention of the respiratory distress syndrome in premature infants (discussed later in detail). There are few examples of attempts at the prenatal treatment of genetically determined metabolic defects, however. What follows is a discussion of three inborn metabolic errors affecting fetal development for which in utero fetal therapy has been attempted with varying success. We will also briefly discuss several animal models of unusual metabolic disorders for which novel antenatal therapies are being evaluated and that may someday be available for the treatment of affected human fetuses.

Congenital Adrenal Hyperplasia

The fetal adrenal glands can be pharmaceutically suppressed by maternal replacement doses of dexamethasone.[19] In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, there is impairment in the metabolic pathway from cholesterol to cortisol that creates both an excess of the metabolic intermediary 17-hydroxyprogesterone and a deficiency of cortisol. The excess 17-hydroxyprogesterone is metabolized by an alternative pathway, creating excessive androstenedione and other adrenal androgens. The absence of cortisol results in a lack of feedback inhibition of the hypothalamus, and high levels of corticotropin (ACTH) are produced. Elevated levels of corticotropin stimulate further activity in the adrenal gland and an exacerbation of the 17-hydroxyprogesterone excess, leading to still more adrenal androgen production. Consequently, genetic female fetuses are exposed to excess androgens and become masculinized. The abnormal genital differentiation can vary from clitoral hypertrophy to the complete formation of a phallus with an apparent scrotum.

In an attempt to prevent this defect, Evans and colleagues administered dexamethasone, a potent corticosteroid, to an at-risk mother beginning in the 10th week of gestation.[19] The rationale of such therapy was to replace feedback inhibition of the fetal hypothalamus, thereby eliminating excessive 17-hydroxyprogesterone production and the attendant overproduction of adrenal

*See K. J. Moise, Jr, MD, "Intrauterine Transfusion With Red Cells and Platelets," on pages 318-324.

androgen. Maternal estriol and cortisol levels indicated rapid and sustained fetal and maternal adrenal gland suppression. The fetus turned out to be a carrier.

Following these initial observations, Forest and David used the same protocol of administering 0.25 mg of dexamethasone orally to the mother four times a day beginning at 9 weeks' gestation to treat several fetuses.[20] They subsequently reported that the in utero dexamethasone-treated fetuses known to be clinically affected with the severe form of 21-hydroxylase-deficient adrenal hyperplasia were prevented from having external masculinization.[20,21] To date, several infants with classic congenital adrenal hyperplasia who clearly would have been masculinized have been born with normal genitalia. In a few cases, some masculinization has still been observed after this regimen was used beginning at 9 weeks. Our current protocol, therefore, is to begin at 7 weeks, although there have been too few cases to assess the results of this modification.[22,23] These events represent the first pharmacologic prevention of a birth defect and may serve as a model for other attempts at fetal therapy for congenital metabolic errors in which abnormal changes begin in utero.

Methylmalonic Acidemia

Methylmalonic acidemia is related to a functional vitamin B_{12} deficiency. Coenzymatically active vitamin B_{12} is required for the conversion of methylmalonyl coenzyme A to succinyl coenzyme A. Genetically determined causes of methylmalonic acidemia include defects in methylmalonyl-coenzyme A mutase or in the metabolism of vitamin B_{12} to the coenzymatically active form, adenocyanocobalamin, by the converting enzyme. Some patients may respond to the administration of large doses of B_{12}, which can enhance the amount of active holoenzyme (mutase apoenzyme plus adenocyanocobalamin).

Ampola and associates were the first to attempt antenatal therapy for a vitamin B_{12}-responsive variant of prenatally diagnosed fetal methylmalonic acidemia.[24] This disease in fetuses is known to be associated with increased methylmalonic acid excretion in maternal urine. Initial efforts to treat fetuses by high oral vitamin B_{12} intake in the mothers resulted in only marginally decreased maternal urinary methylmalonic acid excretion. When the intravenous administration of 5 mg of cyanocobalamin per day was introduced, however, there was a rise in maternal serum B_{12} levels to more than sixfold over normal, accompanied by a progressive decrease in maternal urinary methylmalonic acid excretion. In fact, maternal urinary methylmalonate levels were only slightly above the normal range when delivery occurred at 41 weeks' gestation. Amniotic fluid methylmalonic acid concentrations that were three times the normal mean at 19 weeks' gestation remained four times the normal mean at term, despite prenatal treatment.

In this instance, prenatal treatment certainly improved the fetal and secondarily the maternal biochemistry. Whether there was any notable clinical benefit to the fetus by in utero treatment cannot be assessed adequately. Reducing the fetal burden of methylmalonic acid should have some beneficial effect on fetal development and should reduce the risks in the neonatal period.[24,25] In the absence of further therapeutic trials, however, this remains only speculation.

Multiple Carboxylase Deficiency

Biotin-responsive multiple carboxylase deficiency is an inborn error of metabolism in which the mitochondrial biotin-dependent enzymes, pyruvate carboxylase, propionyl-coenzyme A carboxylase, and β-methylcrotonyl-coenzyme A carboxylase have diminished activity. Affected patients present as newborns or in the early childhood period with dermatitis, severe metabolic acidosis, and a characteristic pattern of organic acid excretion. Metabolism in patients or in their cultured cells can be restored toward normal with biotin supplementation. There have been two reports of the prenatal administration of biotin to fetuses affected with this disorder.[26,27] In both instances the oral administration of 10 mg per day of biotin to the mothers was followed by the delivery of homozygously affected neonates having no clinical or gross chemical abnormalities.

There is compelling evidence that biotin administration effectively prevents neonatal complications in certain patients with biotin-responsive multiple carboxylase deficiency. No maternal or fetal toxic effects from treatment were observed in either case.[26,27] It is not yet possible to assess definitively the relative advantages or disadvantages of prenatal treatment, although such therapy appears both effective and logical, and further trials seem warranted.

Abnormalities of Mineral Metabolism

The use of specific prenatal mineral supplementation has yet to be reported for the prevention of human fetal disease, but such additives have been used in animals with genetic deficiencies. These animal models are of considerable interest and suggest the possibility of therapy for analogous human genetic diseases.

Manganese. A number of genetic defects with associated pigmentary and inner ear abnormalities occur in animals. Some data suggest that manganese may play a role in modifying the expression of such defects.[28] Hurley and Bell have suggested that a sex-linked form of ocular albinism in humans, associated with labyrinthine dysfunction, may be analogous to some of these disorders in animals.[28] We are unaware of any studies of manganese metabolism in human ocular albinism or of attempts to administer manganese prenatally in the hope of ameliorating the expression of any associated labyrinthine defects.

Copper. Keen and colleagues have investigated the possible amelioration of deleterious effects, by prenatal copper administration, to mice with the autosomal recessive mutant "crinkled" gene.[29] These investigators have suggested that the crinkled gene produces many phenotypic characteristics common to patients with X-linked Menkes' kinky-hair syndrome. Dietary supplementation

of pregnant mice with copper sulfate partially reduced the anticipated phenotypic effects of the gene in homozygous offspring. As has been observed with Menkes' disease (which is refractory to postnatal therapy with copper), postnatal copper supplementation did not increase survival of the crinkled gene mutants. It is therefore conceivable that analogous to the observation of the amelioration of disease in crinkled mutants only by maternal copper supplementation throughout gestation, prenatal copper therapy may be of greater benefit to Menkes'-affected human fetuses as well.

Established Fetal Drug Therapies

Fetal Cardiac Therapy

Although great strides have been made in the diagnosis of fetal cardiac anatomical and functional abnormalities, in utero cardiac therapy currently is limited to the treatment of substantial arrhythmias. In the future, the treatment of some congenital anomalies, particularly valvular anomalies, may be attempted prenatally. The treatment of fetal arrhythmias has had considerable success and is discussed in more detail elsewhere.*

Folic Acid Supplementation and Prevention of Neural Tube Defects

In the United States, the reported overall incidence of neural tube defects ranges from 1 per 600 to nearly 1 per 1,000 live births, with a recurrence rate in first-degree relatives of 2% to 3%.[30(p223)]† Anencephaly is incompatible with life beyond early infancy, and cases of spina bifida are associated with a remarkable degree of morbidity and mortality.[31] With the exception of a small number of cases that can be attributed to pure genetic (mendelian syndromes) or chromosomal abnormalities, the specific pathogenesis of most cases remains unexplained. Epidemiologic data comparing the frequency of neural tube defects among genetically related persons with that of the general population point to a multifactorial model of pathogenesis. That is, there appears to be a genetic predisposition for neural tube defects that is profoundly influenced by environment. This nongenetic component to these disorders allows for the possibility of environmental modification to reduce the risk of these defects.

Epidemiologic studies have demonstrated a wide variation in the prevalence of neural tube defects among different countries, different social and ethnic groups, and from decade to decade in the same population. In many parts of the world, the birth prevalence of neural tube defects has been declining since the 1950s. In the United States, two birth defect surveillance systems, the Nationwide Birth Defect Monitoring Program and the Metropolitan Atlanta Congenital Defects Program, have found a decrease in the rate from 1.3 per 1,000 live births in 1970, to 0.6 per 1,000 births in 1989.[32] This decline strongly suggests the importance of an environmental cause. Several proposed explanations for the decline include population changes in the gene pool, improved and more widespread prenatal diagnostic facilities with selective abortion, and, of particular interest, better maternal nutrition. An association of dietary deficiencies with increased rates of neural tube defects was noted when food was scarce in post-World War II Germany and in Holland following the famine of 1944-1945. In England, the same association has been reported for the lower social classes in which diet was poor.

The possibility that folic acid might be involved was raised in the early 1960s when the administration of a folic acid-deficient diet combined with the folate antagonist, aminopterin, produced neural tube defects in animals. In addition, blood concentrations of folic acid, vitamin C, and vitamin B_{12} were found to be lower on average, and the quality of diet was found to be poorer, among women who gave birth to infants with neural tube defects. This evidence is nonspecific because a deficiency of one nutrient is correlated with the deficiency of other nutrients and of nonnutritional factors. In vitro studies with various nutrients found that only inositol was associated with neural tube defects. Therefore, no clear animal or in vitro evidence exists that vitamin supplementation protects against isolated cases of the disorder.

Human observational data that have been accumulating for the past decade have shown that taking vitamins, including folic acid, in the periconceptional period can reduce the incidence of neural tube defects. Published data are available from randomized and nonrandomized intervention trials and from observational studies. Early studies were conducted only in high-risk groups because of the rarity of the disease, and most of the data have been derived from England where the risk is substantially higher than in the United States. Most of the studies have been retrospective and their results inconclusive.

In 1980 and 1981 the results of two interventional studies were published in which vitamin supplementation around the time of conception was given to women who had a pregnancy with a neural tube defect. The South Wales study was a small, randomized trial of folic acid supplementation alone.[33] The study yielded inconclusive results when it was analyzed according to randomly allocated groups, but a significantly lower recurrence rate occurred in the supplemented group when randomization was ignored. In the second study, which was not randomized,[34] women were given a mixture of eight vitamins including folic acid (0.36 mg per day) in comparison with a control group of already-pregnant women who declined to take the vitamins. The study showed a sevenfold decreased ratio in risk between women taking supplements and those not taking them. This finding, while impressive, has been criticized because of self-selection of the women, an overrepresentation of high risk in the unsupplemented group, and an association between high social class and taking supplements. It therefore appeared that patient selection did introduce some bias to this multicenter study, but it is impossible to assess whether bias ex-

*See M. M. Brook, MD, N. H. Silverman, MD, and M. Villegas, "Cardiac Ultrasonography in Structural Abnormalities and Arrhythmias—Recognition and Treatment," on pages 286-300.

†See also N. C. Rose, MD, and M. T. Mennuti, MD, "Maternal Serum Screening for Neural Tube Defects and Fetal Chromosome Abnormalities," on pages 312-317.

plains all the results. There may also have been a direct preventive effect, and it was not known whether the responsible component was folic acid or one of the other vitamins.

Clearly there was a need to solve the problem by a large, randomized, double-blind intervention trial, which was launched in July 1983 by the British Medical Research Council and involved 33 centers.[35] The study was halted in 1991 by the ethical committee after abundant information and clear results were obtained on this issue, so that all women at risk could receive the possible benefits of the supplementation. The population tested was a high-risk group of women who had a previous pregnancy with a neural tube defect and who were randomly assigned to one of four supplementation groups: group A received 4.0 mg of folic acid, group B a multivitamin preparation also containing 4.0 mg of folic acid, group C neither multivitamins nor folic acid, and group D multivitamins without folic acid. To test the effect of folic acid, they compared the outcomes of groups A and B with those of groups C and D. To test the effect of multivitamins, the researchers compared the outcomes in groups B and D with those of groups A and C. The results of this study showed that high doses of folic acid reduced the risk of having a subsequent pregnancy with a neural tube defect by 70%, which is a threefold ratio. The study also showed that folic acid is an effective agent that avoids the need to use a mixture of vitamins with the concern over the possible toxicity of other vitamins.

Several relevant questions remain to be answered. No trial to date has been designed to demonstrate the relative efficacy of different doses or to answer the important question of what is the minimal effective dose of folic acid. Similarly, no present study has enough power to address the question of safety using high doses of folic acid for public health purposes.

The fact that 95% of the cases of neural tube defects occur in the low-risk general population raises the last and most important question: Are the results of studies restricted to the high-risk group (those mothers with a history of affected offspring) generalizable to the low-risk group? To determine whether periconceptional vitamin supplementation could reduce the incidence of a first occurrence of neural tube defects, four observational studies and one recent nonrandomized interventional Cuban study were done and the results published.[36-40] All but one showed a lower risk for the first occurrence of a neural tube defect in the general population for women who consumed 0.4 to 0.8 mg per day of folic acid from multivitamin supplementation, but all were criticized for possible selection and recall bias. Recently the results of a carefully designed, prospective, randomized controlled trial of multivitamin and mineral periconceptional supplementation (including 0.8 mg per day of folic acid) involving almost 5,000 Hungarian women who had not had a previous neural tube defect-affected pregnancy was reported.[41] This study was halted before its intended completion because of the clear evidence of a protective effect.

When data from several studies are synthesized, they suggest that folic acid alone at doses of 0.4 mg per day will reduce the risk of neural tube defects. The anticipated reduction in the United States has been reasonably estimated at 50%. Based on these data, the US Public Health Service has recommended that all women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg per day of folic acid for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other neural tube defect.[42] Women who have had an affected pregnancy should consume 0.4 mg of folic acid per day, unless they are planning a pregnancy. In that case they can follow the August 1991 guideline from the Centers for Disease Control[43] and consult their physician about the desirability of using 4.0 mg of folic acid per day. This recommendation comes from the Medical Research Council data, which is felt to be the most rigorous study directed at this high-risk group and in which that was the only dose tested. Because of the well-known potential of high-dose folic acid supplementation to exacerbate the effect and to complicate the diagnosis of vitamin B_{12} deficiency, it has been suggested that the consumption of greater than 1 mg per day be carefully supervised by a physician.

Pharmaceutic Induction of Fetal Lung Maturity

Preterm delivery is a major cause of perinatal morbidity and mortality in the industrialized countries of the world. Despite recent advances in the respiratory care and management of premature infants, the respiratory distress syndrome is still a major cause of morbidity and mortality, including the sequelae of intracranial hemorrhage and chronic pulmonary disease.

Impaired or delayed surfactant synthesis appears central to the pathogenesis of the respiratory distress syndrome.[44] Various pharmaceutic agents are known to influence surfactant synthesis and possibly other aspects of lung development. These include corticosteroids, thyroid hormone, thyrotropin-releasing hormone (TRH), prolactin, insulin, aminophylline, and β-agonists. Since the introduction of surfactant to the arsenal of agents for the treatment and prevention of respiratory distress syndrome, it is now possible to combine hormonal therapy before delivery and surfactant administration after birth for the best possible drug intervention.

Corticosteroids

Corticosteroids have many effects on developing lungs. Some of the important ones evidenced by in vitro data and studies of animals are as follows:

- Increased synthesis of phosphatidylcholine (a major constituent of lung surfactant) and other phospholipids;
- Increased levels of surfactant apoproteins that have been documented to enhance surfactant reuse;
- Accelerated structural maturation of the fetal lung, as well as influence on lung collagen and elastin synthesis that may be responsible for improved lung distensibility;

- Increased β-receptor density in fetal lung;
- Decreased alveolar protein leak; and
- Increased pulmonary antioxidant enzyme activity

that might have a protective effect on newborn lungs from oxygen toxicity.

Of several controlled randomized trials on the neonatal outcomes of corticosteroid administration before preterm delivery, the largest was from a collaborative group on antenatal steroid therapy in which 696 women at risk and their pregnancy outcomes were evaluated.[45] Most studies show similar results using dexamethasone, betamethasone, hydrocortisone, or methylprednisolone, although the first two agents were most commonly used. Accumulated data from the controlled trials, involving more than 3,000 participants, have shown that antenatal corticosteroid administration leads to a statistically significant and clinically relevant reduction in neonatal mortality and respiratory morbidity.[46] The beneficial effects have been manifested in babies at risk for the respiratory distress syndrome born at all gestational ages, whether or not there has been rupture of membranes.[47] Other benefits that appear to be associated with corticosteroid administration are reduced incidences of intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death.

Several possible risks of high-dose corticosteroid therapy have been reported. The theoretical risk of maternal as well as fetal and neonatal infection may be increased if steroids are administered following prolonged rupture of membranes, although this has not been strongly apparent in studies addressing this issue.[46] An association of the development of pulmonary edema in pregnant women receiving a combination of steroids and tocolytic drugs has been reported.[48] There has also been a debate over a possible adverse effect of corticosteroid therapy on the evolution of preeclampsia.[49] In summary, however, with proper patient selection and intensive antenatal and neonatal care, most investigators believe that the demonstrated advantages of antenatal steroid therapy outweigh the mostly theoretical risks.

Thyroid Hormones

Thyroid hormones play a role in fetal lung maturation. From studies of animals it appears that thyroid hormones increase surfactant synthesis, accelerate the structural development of the lungs, decrease the alveolar capillary protein leak, and generally improve lung function. Because thyroxine and triiodothyronine are poorly transported across the placenta, intra-amniotic instillation of thyroxine has been used in clinical trials with promising results.[50] This approach relies on fetal absorption, however (which depends on fetal swallowing and amniotic fluid volume), making dosimetry problematic.

A second approach involves stimulating endogenous fetal production of triiodothyronine and thyroxine by thyrotropin-releasing hormone, which is known to readily cross the placenta. An added possible benefit of exogenous TRH is its ability to stimulate fetal prolactin production. Prolactin has been reported to have its own potentiating effect on fetal lung maturation. With this rationale, a randomized study has been published on the combined use of corticosteroids and TRH compared with corticosteroids alone.[51] Combined therapy was associated with a greater rate of post-therapy improvement in the lecithin-sphingomyelin ratio, significantly decreased the number of days in the neonatal period requiring respiratory support, and lowered the incidence of bronchopulmonary dysplasia. Although this report is encouraging, additional studies are needed to confirm and characterize the effect before thyroid hormones are likely to be widely accepted.

Other Agents Affecting Fetal Lung Maturation

Aminophylline. In vitro studies and those in animals have shown positive effects of aminophylline on fetal lung maturation. Clinical trials are limited, although one study reported a reduced incidence of the respiratory distress syndrome in newborns of aminophylline-treated mothers compared with a control group.[52] Further studies are needed before any conclusion can be made.

β-Adrenergic agents. There is some evidence that β-adrenergic stimulation enhances surfactant secretion from type II alveolar cells of the fetal lung. Because these agents are so extensively used in obstetrics to inhibit preterm labor, it is difficult to assess their additional benefit in preventing the respiratory distress syndrome.

Ambroxol. Ambroxol, a benzydamine, was developed as a pulmonary expectorant and is widely used in Europe. Its use has been shown to stimulate surfactant production and secretion by type II alveolar cells, although its mechanism of action is not completely understood. A multicenter, randomized Italian study compared antenatal therapy using betamethasone with that of ambroxol for the prevention of the respiratory distress syndrome.[53] The incidence of the disorder was 13% in the ambroxol-treated group compared with 31% in the group receiving betamethasone. The authors concluded that ambroxol is at least as effective as steroids for preventing the respiratory distress syndrome. Further clinical and experimental evaluation of this promising drug is needed and ongoing.

The Future

Advances in technology, while not entirely predictable, can be expected to produce new therapeutic agents for the treatment of cardiac arrhythmias, more precise biologic replacement levels of missing hormones such as in 21-hydroxylase-deficient congenital adrenal hyperplasia, vitamin and mineral supplements for a number of disorders, and improved steroid therapy for fetal lung maturation. The concomitant developments of enhanced surgical techniques and molecular genetic diagnosis make it likely that there will be improved access to fetuses and more precise diagnoses available that will allow for targeted treatments using all three approaches: surgical, drug, and genetic. The future appears bright, although it is impossible to predict the rate at which each of these areas will develop.

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